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Trends in Morbidity and Mortality of Hepatic Resection for Malignancy

A Matched Comparative Analysis

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Objective
The authors define more clearly the trends in morbidity and mortality after hepatic resection for malignant disease in matched patient groups during two discrete time periods.

Summary Background Data
Recent reports have shown improvement in operative morbidity and mortality associated with hepatic resection; however, results often included resections for benign disease and trauma. Furthermore, specific factors contributing to the improvement in operative risks between the last two decades have not been defined.

Methods
A retrospective matched comparative analysis was conducted of patients with primary and metastatic hepatic malignancy resected with curative intent between two periods (1976 to 1980 and 1986 to 1990). Eighty-one patients met our inclusion criteria in the early period; this group was matched with 81 patients from the latter period by the following four parameters: age, gender, type of malignant disease, and extent of resection. Records of these two patient groups were abstracted for clinical presentation, co-morbid factors, operative techniques, and perioperative morbidity and mortality.

Results
The authors found a significant decrease in operative morbidity, median perioperative transfusion, and length of hospital stay in the latter period (1986 to 1990). The incidence of postoperative subphrenic abscess and intra-abdominal hemorrhage was significantly lower during this period. Operative mortality rate was similar for both periods, 4.9% and 1.2%, respectively ($p > 0.05$).

Conclusion
Hepatic resection for malignant disease currently can be performed with a low morbidity and mortality in the hands of trained and experienced hepatic surgeons; operative risks of hepatic resection should not deter its application in the treatment of primary and metastatic malignant diseases of the liver.

Historically, significant perioperative mortality and unproven benefits of resection often deterred surgical intervention for malignant diseases of the liver.[1,2] Recent advances in the understanding of hepatic anatomy and physiology, together with improvements in perioperative management, have contributed to a reduction in morbidity and mortality associated with hepatic resection.[3-5] Recent literature shows that patients who undergo resection of hepatic malignancy with curative intent have an increased survival compared with patients in whom resection is deferred.[6-8] Although a relationship between increased survival and resection continues to evolve, full understanding and characterization of the improvements in morbidity and mortality of hepatic resection for malignancy remain incomplete.[2] Many reports[8-15] include the risks of hepatic resection for benign disease and trauma, which differ from that for malignant disease. Hepatic resection or debridement for trauma is associated with a higher mortality because of complications from shock, multiple transfusions, and concomitant multiorgan injuries.[5,12,14-17] Hepatic resection in patients with concurrent hepatobiliary sepsis, i.e., obstructing hilar cholangiocarcinoma or hepatolithiasis, also has significant mortality.[9] In contrast, operative risks for benign hepatic diseases are minimal.[9,12,15] Several studies between 1970 and 1990 show operative mortality ranging from 8.5% to 19% for primary hepatic malignancy and 6.3% to 11% for metastatic hepatic malignancy.[18-26] However, specific changes in operative morbidity and mortality between these two decades has not been addressed. The aim of this study is to define more clearly the trends in morbidity and mortality after hepatic resection for malignancy in matched patient groups during two discrete time periods.

PATIENTS AND METHODS

Medical records of all patients who underwent hepatic resection for malignant diseases of the liver from 1976 to 1980 (n = 130) and from 1986 to 1990 (n = 475) were reviewed retrospectively. These records were abstracted for age, gender, type of hepatic malignancy, and extent of hepatic resection, but were blinded to operative outcome. The diagnosis of malignancy was based on the pathologic findings of the resected hepatic tumor. We excluded diagnostic biopsies, resections for carcinoid tumors, pediatric tumors, and en bloc resections with adjacent intra-abdominal malignancies, i.e., carcinoma of the extrahepatic bile duct, gallbladder, stomach, colon, and adrenal gland. Eighty-one patients in the early period who met our inclusion criteria were matched with 81 patients from the latter period by 1) age, 2) gender, 3) type of hepatic malignancy, and 4) extent of hepatic resection. Records of these two matched patient groups were abstracted for clinical presentation, co-morbid factors, operative technique, and perioperative morbidity and mortality.

Major hepatic resection was defined as hemihepatectomy or extended hemihepatectomy. Minor hepatic resection included left lateral sectorectomy, intersegmental wedge resection (> one segment), and intrasegmental wedge resection (≤ one segment).

Operative mortality was defined as death occurring within 30 days of surgery or during the same hospitalization. Operative morbidity was defined as any complication occurring within the same interval, exclusive of mortality. Perioperative transfusion was defined as transfusion of whole blood or packed red blood cells intraoperatively or within 48 hours of operation. Operative time was defined as time of skin incision to completion of skin closure.

Statistical analysis was performed using rank sum test and chi square test. Differences were considered significant if $p < 0.05$.

RESULTS

Demographics and Clinical Findings

Table 1 shows the distribution of patient gender and age, type of malignancy, and extent of resection of the matched patients in both groups. Table 2 summarizes the clinical presentation and co-morbid factors of both patient groups. More patients presented with abdominal mass and weight loss between 1976 and 1980. The prevalence of co-morbid factors was similar between time periods.

Conduct of Operation

More patients underwent a thoracoabdominal incision in the early period (54% *vs.* 22%; $p < 0.0001$). Hepatic hilar dissection before parenchymal transection was performed routinely for major hepatic resections. The techniques and frequency of hepatic hilar dissection were unchanged between the two periods. Isolation or ligation of the hepatic veins before resection was performed in 33% of the patients in the early period and 24% in the latter period ($p > 0.05$). Vascular inflow occlusion via clamping of the hepatoduodenal ligament

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Table 1. DEMOGRAPHICS

	1976–1980 n = 81	1986–1990 n = 81	p Value
Age (yrs)			
Median	59	59	NS
Range	17–82	17–82	NS
Gender (no.)			
Men	51	51	NS
Women	30	30	NS
Malignancy (no., %)			
Primary	29 (36)	21 (26)	NS
HCC	22 (27)	19 (23)	
Cholangiocarcinoma	5 (6)	2 (3)	
Angiosarcoma	1 (1)	0	
Cystadenocarcinoma	1 (1)	0	
Metastatic	52 (64)	60 (74)	NS
Colorectal	49 (61)	56 (69)	
Pancreatic islet cell	2 (3)	2 (3)	
Leiomyosarcoma	1 (1)	2 (3)	
Extent of resection (no., %)			
Major	40 (49)	41 (51)	NS
Hemihepatectomy	26 (32)	34 (42)	
Extended hemihepatectomy	14 (17)	7 (9)	
Minor	41 (51)	40 (49)	NS
Left lateral sectorectomy	5 (6)	8 (10)	
Intersegmental wedge	22 (27)	18 (22)	
Intrasegmental wedge	14 (17)	14 (17)	

NS = Not significant.

Table 2. CLINICAL PRESENTATION AND COMORBID FACTORS

	1976–1980 No. of Patients (%)	1986–1990 No. of Patients (%)	p Value
Clinical presentation			
Abdominal mass	29 (36)	14 (17)	<0.01
Weight loss	18 (22)	11 (13)	<0.05
Pain	30 (37)	23 (28)	NS
Malaise	11 (14)	7 (9)	NS
Fever/night sweats	5 (6)	6 (7)	NS
Jaundice	1 (1)	0	NS
Comorbid factors			
Cirrhosis	3 (4)	1 (1)	NS
Chronic active hepatitis	1 (1)	0	NS
Hemachromatosis	0	1 (1)	NS
Previous abdominal surgery	60 (74)	60 (74)	NS
Tobacco use	12 (15)	6 (7)	NS
Alcohol abuse	7 (9)	5 (6)	NS
Ischemic heart disease	6 (7)	7 (9)	NS
Peptic ulcer disease	6 (7)	3 (4)	NS
COPD	3 (4)	4 (5)	NS
Steroid use	2 (3)	2 (3)	NS
Diabetes	1 (1)	2 (3)	NS

NS = Not significant.
COPD = Chronic obstructive pulmonary disease.

was used infrequently (5% and 10%, respectively; $p > 0.05$).(Table 3).

We began using the Cavitron Ultrasonic Surgical Aspirator ([CUSA], Valley Lab Inc., Stamford, CT) for hepatic parenchymal transection in November 1987. The CUSA was used in 15% of the patients in the latter period. Other techniques of parenchymal transection included electrocoagulation combined with blunt dissection using a scalpel handle, hemostat, or suction tip. Mean operative time was 220 minutes in the early period and 227 minutes in the latter period.

Drains were placed in 91% of the patients in the early period and 93% in the latter period ($p > 0.05$). Closed suction drains were used during both periods except for two patients in the early period in whom Penrose drains were placed. Mean duration of drainage was 8 days and 6 days, respectively ($p > 0.05$).

Concomitant Resection of Diaphragm, Colon, or Lung

Twelve per cent of the patients in the early period required resection of a portion of the diaphragm involved with tumor compared with 5% in the latter period ($p < 0.05$). Of the patients who underwent hepatic resection for colorectal metastases, more patients underwent synchronous hepatic and colon resection in the early period

Table 3. CONDUCT OF OPERATION

	1976–1980 No. of Patients (%)	1986–1990 No. of Patients (%)	p Value
Incision			
Abdominal	37 (46)	63 (78)	<0.0001
Thoracoabdominal	44 (54)	18 (22)	<0.0001
Preresection			
Hilar dissection	39 (48)	41 (51)	NS
Hepatic vein ligation	27 (33)	19 (24)	NS
Vascular inflow occlusion	4 (5)	8 (10)	NS
CUSA	0	12 (15)	<0.0001
Drain	75 (93)	76 (94)	NS
Operating time (min, mean)	220	227	NS

CUSA = Cavitron Ultrasonic Surgical Aspirator; NS = not significant.

Table 4. INTRAOPERATIVE FLUID INFUSION AND PERIOPERATIVE TRANSFUSION

	1976–1980	1986–1990	p Value
Crystalloid, liters	2.0	4.8	<0.0001
Transfusion			
Median units	2	0	<0.001
No. of patients transfused (%)	65 (80)	34 (42)	<0.0001

(20% *vs.* 9%; $p < 0.05$). Concomitant hepatic and lung resections for colorectal metastases were performed in three patients (4%) in the early period and none in the latter period ($p < 0.05$).

Intraoperative Fluid Infusion and Perioperative Blood Transfusion

A balanced electrolyte solution with glucose (D_5LR) was used intraoperatively in both periods. Whole blood was given in the early period; packed red blood cells were given in the latter period. Data on volume of intraoperative fluid infusion and perioperative blood transfusion are shown in Table 4.

Median Hospital and Intensive Care Unit Stay

Table 5 compares the of length of stay in the hospital and the intensive care unit between the two periods.

Reoperation

The reoperation rate was not different between periods (5 *vs.* 3 patients). Indications for reoperation in the early period were hemorrhage (n = 3) and subphrenic abscess (n = 2). Indications for reoperation in the latter period were bile leak (n = 1), gastric outlet obstruction (n = 1; this patient had chronic peptic ulcer disease), and acute abdomen (n = 1; this patient was found intraoperatively to have portal vein thrombosis).

Table 5. LENGTH OF STAY IN HOSPITAL AND INTENSIVE CARE UNIT

	1976–1980 Days	1986–1990 Days	p Value
Hospital stay (median)	11	9	<0.001
ICU stay (median)	2	0	<0.0001

Mortality

Perioperative mortality was not different between the periods (4.9% *vs.* 1.2%, respectively; $p > 0.05$). Causes of death for the four patients in the early period were multiorgan failure, pulmonary embolism, hemorrhage, and sepsis, respectively. The one death in the latter period was from multiorgan failure.

Morbidity

Postoperative complications occurred in 28 of 77 surviving patients (36.3%) in the early period and 13 of 80 surviving patients (16.2%) in the latter period ($p < 0.01$). Forty-five complications occurred in 28 patients in the early period; twenty-five complications occurred in 13 patients in the latter period. Complications were subdivided into intra-abdominal, pulmonary, and miscellaneous. Intra-abdominal complications developed in more patients during the early period, 23% *versus* 9% ($p = 0.01$); specifically, there was a higher incidence of subphrenic abscess, small bowel obstruction, and hemorrhage. The incidence of bile leak was the same for both periods. The occurrence of pulmonary complications, including atelectasis, pleural effusion, pneumonia, hemothorax, and empyema, were not significantly different between periods. Miscellaneous complications, including transfusion-requiring coagulopathy, persistent hyperbilirubinemia (elevated bilirubin for longer than 3 weeks postoperatively), cardiac dysrhythmia, deep venous thrombosis, wound infection, drain tract infection, urinary tract infection, and brachial plexus injury, were not significantly different between the two periods. Injuries to the brachial plexus were unique to patients positioned for thoracoabdominal incisions. The number of these complications alone were too few for comparative statistical analysis (Table 6).

DISCUSSION

The aim of our study was to define more clearly the changes in operative morbidity and mortality of hepatic resection for malignant disease between the last two decades. In matched patient groups with similar co-morbid factors undergoing hepatic resection for malignancy, we observed several differences between the two study periods.

During the early period (1976–1980):

- More patients had abdominal mass or weight loss at

Table 6. COMPLICATIONS

Complications	No. of Patients 1976–1980 n = 77	No. of Patients 1986–1990 n = 80	p Value
Intra-abdominal	18 (23.3)	7 (8.6)	0.01
Subphrenic abscess	6 (7.8)	0	
Bowel obstruction	5 (6.5)	0	
Bile leak	3 (3.9)	4 (5.0)	
Hemorrhage	2 (2.6)	0	
Presacral abscess	1 (1.3)	0	
Cholangitis	1 (1.3)	0	
Ascites	0	1 (1.3)	
Sterile perihepatic fluid collection	0	1 (1.3)	
Gastric outlet obstruction	0	1 (1.3)	
Pulmonary	10 (13.0)	5 (6.3)	>0.05
Atelectasis	5 (6.5)	1 (1.3)	
Pleural effusion	3 (3.9)	2 (2.5)	
Pneumonia	1 (1.3)	1 (1.3)	
Hemothorax	1 (1.3)	0	
Empyema	0	1 (1.3)	
Miscellaneous	13 (16.9)	9 (11.3)	>0.05
Coagulopathy	4 (5.2)	5 (6.3)	
Persistent hyperbilirubinemia	1 (1.3)	1 (1.3)	
Cardiac dysrhythmia	2 (2.6)	0	
Deep-vein thrombosis	0	1 (1.3)	
Wound infection	1 (1.3)	0	
Drain tract infection	2 (2.6)	0	
Urinary tract infection	1 (1.3)	2 (2.5)	
Brachial plexus injury	2 (2.6)	0	

presentation or had malignant involvement of the diaphragm at operation.

- More patients underwent a thoracoabdominal incision.
- More patients underwent concomitant resection of a primary colorectal carcinoma or a lung metastasis.
- Postoperative intensive care unit monitoring was used for a greater number of patients.
- The median hospital stay was longer.

During the latter period (1986–1990):

- The ultrasonic surgical aspirator came into use for hepatic parenchymal resection.
- More crystalloid was given during operation.
- Fewer patients received blood transfusions, and less blood was transfused per patient during the perioperative period.
- The incidences of postoperative subphrenic abscess, intra-abdominal hemorrhage, and bowel obstruction were decreased significantly.
- Mortality was lower, but not significantly changed from the early period.

Review of western literature of patients undergoing hepatic resection for malignant diseases[3–4,21,25–26] (Table 7) showed that operative mortality decreased between the last two decades; however, morbidity remained about the same. Our data also showed a decrease in operative mortality from 4.9% to 1.2% between the two decades, although this difference is not statistically significant. Furthermore, our experience showed a significant decrease in operative morbidity from 36.6% to 16.2%. Reported lengths of operation have not been significantly different between decades (4.25 to 6.5 hrs *vs.* 4.25 to 7.5 hrs).[3–4,21,25,26] Our data showed a shorter operating time but no difference between the two periods. Estimated operative blood loss from the literature ranged from 3000 mL to 3080 mL between 1970 and 1980.[3,4] Published data on blood loss between 1980 and 1990 are not available; however, median intraoperative transfusion ranged from 0 to 5.5 units.[21,25–26] Our data reflect a significant decrease in median perioperative transfusion between decades (2 units *vs.* 0 units). The length of hospital stay was significantly shorter between 1980 and 1990 in both the literature and our experience.

Table 8 summarizes postoperative complications by decade from review of the literature.[3,4,21,25,26] Between

Table 7. PERIOPERATIVE OUTCOME AFTER HEPATIC RESECTION FOR MALIGNANT DISEASES OF THE LIVER: REVIEW OF WESTERN LITERATURE

Year/Author	n	Mortality (%)	Morbidity (%)	Operating Time (hrs)	Blood Loss (mL)	Perioperative Transfusion (units)	Hospital Stay (days)
1970–80							
1970–75 Fortner[3]	55	17	—	6.50	—	—	18
1971–78 Bengmark[4]	18	11	25	4.25	3080	—	24
1975–80 Fortner[3]	82	6	—	4.75	3000	—	13
1976–80 Current study	81	4.9	32	3.75	—	2	11
1980–1990							
1980–85 Delva[21]	142	5.6	32	4.25	—	5.5	17.7
1984–89 Cole[25]	43	0	23	7.50	—	5.4	15
1988–90 Jamieson[26]	75	1.2	13.5	—	—	0	10
1986–90 Current study	81	1.2	16	3.78	—	0	9

1970 and 1980, the most frequent complications were subphrenic abscess, pleural effusion, and wound infection. These remain the most common complications between 1980 and 1990; however, there has been a significant decrease in the frequency of these complications. Similarly, the incidence of intra-abdominal hemorrhage decreased from 5.2% to 0.8% between decades.

Table 8. OPERATIVE MORBIDITY AFTER HEPATIC RESECTION FOR MALIGNANT DISEASE: REVIEW OF LITERATURE

Complications	Bengmark,[3] Fortner[4] (1970–1980) (N = 155) Percent	Delva,[21] Cole,[25] Jamieson[26] (1980–1990) (N = 260) Percent
Intraabdominal		
Subphrenic abscess	16.8	6.2
Intraabdominal hemorrhage	5.2	0.8
Gastrointestinal hemorrhage	1.9	1.9
Bile leak	1.9	0.4
Enterocutaneous fistula	1.3	0
Main bile duct injury	1.3	0
Portal vein thrombosis	0.6	0
Pulmonary complications		
Pleural effusion	14.2	6.9
Pneumonia	1.3	0
Hemothorax	0.6	0.4
Pneumothorax	0.6	0
Atelectasis	0	1.9
Miscellaneous		
Wound infection	6.5	3.5
Deep-vein thrombosis	3.2	0.8
Transfusion hepatitis	1.3	0
Acute renal failure	0.6	0
Hepatorenal syndrome	0.6	1.5
Wound dehiscence	0	0.8

In this study, subphrenic abscess was the most common complication between 1976 and 1980. It was the cause of reoperation in two patients, one of whom subsequently died of continued sepsis. Between 1986 and 1990, only one patient had a sterile perihepatic fluid collection, which was treated successfully by percutaneous drainage. The incidence of postoperative intra-abdominal hemorrhage decreased from 3% to 0 between our study periods. During the early period, it was the cause of reoperation in three patients, one of whom died from continued hemorrhage secondary to coagulopathy.

The management of intra-abdominal sepsis and hemorrhage has undergone a transition during the last decade. Computed tomography and ultrasound-guided percutaneous aspiration with and without placement of drainage catheters for subphrenic abscess or hematoma have been reported with favorable results.[14] Careful selection of patients who can be managed adequately by percutaneous drainage of intra-abdominal collections may avoid the risks of operative drainage and improve the overall morbidity and mortality associated with hepatic surgery.

Three conclusions can be drawn from our experience and review of the literature regarding trends in morbidity and mortality of hepatic resection for malignancy. First, significant decreases have occurred in the volume of perioperative blood transfusion and the incidences of subphrenic abscess and intra-abdominal hemorrhage. Second, the overall improvement in morbidity and mortality associated with hepatic resection probably reflects the decreased incidence of intra-abdominal sepsis and

hemorrhage. Third, major hepatic resection for malignant disease can be performed safely with minimal morbidity and mortality.

With state-of-the-art surgical techniques and perioperative management, the operative morbidity and mortality associated with elective hepatic resection for malignant diseases are low. Many of the complications, e.g., bile leak, pleural effusion, and coagulopathy, often resolve spontaneously or require minimal intervention. With the advent of percutaneous drainage for subphrenic abscess, this major complication often can be managed with less morbidity. Advances in liver surgery currently permit what used to be a formidable procedure with high morbidity and mortality to become one that can be performed with certainty of vascular control and minimal hemorrhage. Hepatic resection in the 1990s is a safe and controlled procedure in the hands of experienced hepatic surgeons. Operative risks of hepatic resection should not deter its application in the treatment of primary and metastatic malignant disease of the liver.

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